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### Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men

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**Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia**

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**Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia**

Short running title: Sex differences in diabetes-related risk of dementia

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**ABSTRACT**

**Objective:** Type 2 diabetes confers a greater excess risk of cardiovascular disease in women than in men. Diabetes is also a risk factor for dementia but whether the association is similar in women and men remains unknown. We performed a meta-analysis of unpublished data to estimate the sex-specific relationship between diabetes with incident dementia.

**Research Design and Methods:** A systematic search identified studies published prior to November 2014 that had reported on the prospective association between diabetes and dementia. Study authors contributed unpublished sex-specific relative risks (RR) and 95% confidence intervals (95% CI) on the association between diabetes and all dementia and its subtypes. Sex-specific RRs and the women-to-men ratio of RRs (RRRs) were pooled using random-effects meta-analyses.

**Results:** Study-level data from 14 studies, 2,310,330 individuals and 102 174 dementia cases were included. In multiple-adjusted analyses, diabetes was associated with 60% increased risk of any dementia in both sexes: pooled RR (95% CI) 1.62 (1.45-1.80) in women, and 1.58 (1.38-1.81) in men, respectively. The diabetes-associated RRs (95% CI) for vascular dementia were 2.34 (1.86-2.94) in women and 1.73 (1.61-1.85) in men, and for non-vascular dementia were 1.53 (1.35-1.73) in women and 1.49 (1.31-1.69) in men. Overall, women with diabetes had 19% greater risk of developing vascular dementia than men: multiple-adjusted RRR 1.19 (1.08-1.30)  $p < 0.001$ .

**Conclusions:** Individuals with type 2 diabetes are at approximately 60% greater risk of developing dementia compared with those without diabetes. For vascular, but not for non-vascular dementia, the additional risk is greater in women.

Dementia is a multi-faceted syndrome that lays claim to a growing burden of global disease: the most recent estimates suggest that there are approximately 44 million affected individuals worldwide and a further 7.7 million new cases annually.<sup>1, 2</sup> Underpinned by a shifting demographic and associated epidemiological profile worldwide, the prevalence of dementia is forecast to nearly double by 2030, and to triple by 2050, and is set to create a significant economic, social and public health burden particularly in resource-poor countries.<sup>1, 2</sup>

Non-vascular dementia, which mainly constitutes Alzheimer's disease (AD), and vascular dementia are the two most common forms of dementia, accounting for about 70% (25 million) and 20% (7 million) of all dementia cases, respectively.<sup>2</sup> Lifestyle risk factors including type 2 diabetes, cigarette smoking, and obesity are associated with an increased risk of developing both vascular dementia and non-vascular dementia in later life.<sup>3</sup> For example, a review that included information on approximately 15,000 cases of dementia, found that, compared to non-affected individuals, those with diabetes had roughly 70% greater risk of developing dementia.<sup>4</sup>

While of value, this review has some important limitations<sup>4</sup>: over 73% of dementia cases were derived from two large Asian cohorts,<sup>5, 6</sup> and the influence of these studies on the overall summary estimates was not examined. Moreover, information on dementia subtypes was not universally available, including the single study that provided information on more than 50% of all dementia cases.<sup>5</sup> Finally, as the analyses were not sex-specific it was not possible to determine whether the magnitude of the association between diabetes and incident dementia and its main subtypes differed in women and men. This is of interest



given the substantial amount of evidence suggesting that diabetes confers a significantly greater additional vascular hazard in women compared with men which potentially has ramifications for the clinical management of diabetes and vascular disease in women.<sup>7-9</sup>

To overcome the substantial methodological limitations of past reviews, we requested individual study investigators to contribute unpublished results to a pooled analysis. In line with the current evidence base which suggests that diabetes poses more of a vascular hazard in women compared with men, our hypothesis was that diabetes confers a greater excess risk of vascular dementia in women than in men but that the impact of diabetes on risk of non-vascular dementia is similar between the sexes.

## RESEARCH DESIGN AND METHODS

### *Search strategy and selection criteria*

We used PubMed MEDLINE ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)) and OVID MEDLINE for the period from January, 2011 to November, 2014 to identify studies that had reported on the association between diabetes and dementia in men and women from a general population. The search strategy combined the following text terms and MeSH: 'dementia', 'vascular dementia', 'delirium', 'cognitive disorders', 'amnesic disorders', 'frontotemporal dementia', 'multi-infarct dementia', 'Alzheimer disease', 'Lewy body', 'type 2 diabetes mellitus', 'diabetes mellitus', 'DM', 'diabetes complications', 'blood glucose', 'impaired glucose tolerance', 'glycosylated hemoglobin', and 'prediabetes'. Studies prior to 2011 were identified from previous systematic reviews.<sup>4, 10, 11</sup> Data from randomized trials were excluded due to the non-generalizable nature of trials to the general population. Two authors (SAEP and SC) conducted the literature search. Uncertainties regarding the identification of studies were

discussed and resolved by mutual consent. Since most studies did not publish estimates of relative risk separately for men and women or for dementia subtypes, and varied by which factors were included in adjusted models, we contacted authors of all the selected studies and asked them to provide additional results adjusted, where possible, for the same set of confounders: blood pressure, cigarette smoking, body mass index and total cholesterol. On a specifically designed form, contributing authors provided summary results for the age- and multiple-adjusted relative risks (RRs) and 95% confidence intervals (CIs) for any dementia, and if available, for vascular dementia and non-vascular dementia segregated by sex.

#### *Data extraction and statistical analysis*

The primary endpoints were incident all-cause dementia, vascular dementia, and non-vascular dementia (as defined by the study investigators: see Supplementary Table 1). The primary metrics were the pooled multiple-adjusted RRs for dementia associated with diabetes and the women-to-men ratio of the RRs (RRR). Covariates that were included in the multiple-adjusted model were reported differently between studies and are shown in Table 1. Age-adjusted estimates were used in a secondary analysis. From each study, we obtained the previously unpublished sex-specific RRs with accompanying 95% CIs for individuals with versus without diabetes. We also requested information on person-years of follow-up to calculate sex-specific incidence rates in individuals with and without diabetes. We log-transformed these RRs and pooled them across studies using random effects meta-analysis with inverse variance weighting, and then exponentiated these values to obtain the pooled RR separately for women and men. We used similar methods to pool women-to-men ratio of RRs. For each study, we obtained the standard error of the log RRR by taking the square root of the sum of the variance of the two sex-specific log RRs. We used the  $I^2$  statistic to

estimate the percentage of variability across studies due to between-study heterogeneity. In sensitivity analyses, we excluded estimates from two large cohort studies from Taiwan and Korea which had a large influence on the summary estimates.<sup>6, 12</sup> We also examined whether restricting the analysis to those studies that used higher quality research criteria for dementia diagnosis (e.g. the Cross cultural Cognitive Examination, National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association criteria) affected the main results. We explored whether the background rate of dementia in the study population influenced the sex-specific associations by meta-regression analyses of the log RRR versus the difference in incidence rate between women with and without diabetes minus the equivalent estimate in men (i.e. the difference of the difference). We assessed the methodological quality of the studies using the Newcastle-Ottawa Scale (Supplementary methods).<sup>13</sup> All analyses were performed using Stata version 12.0.

## RESULTS

The systematic search identified 1495 unique articles that were subsequently examined on title and abstract (Supplementary Figure 1). Overall, 1425 articles were excluded for one or more reasons including lack of primary data, single-sex population, animal study, non-prospective study design, and randomized trial of a high-risk population. Of the remaining articles, 70 articles qualified for full-text evaluation. Of these, 28 studies had relevant data on the relationship between diabetes and risk of dementia and the authors were contacted and asked to contribute additional estimates to those in the published reports. Authors from 13 studies (response 48%) contributed unpublished summary data,<sup>12, 14-25</sup> and for one study we extracted the necessary data from its published report.<sup>6</sup> The 14 non-contributing

studies comprised 30,900 individuals and 2,300 cases of dementia (Supplementary references) and the baseline characteristics are described in Table 1. Overall, data were available on 2,310,330 individuals (48% women) and 102,174 incident cases of dementia, including 9,253 cases of vascular dementia (52% women) and 90,233 cases of non-vascular dementia (58% women). Three cohorts were from Asia (90% of the individuals),<sup>6, 12, 23</sup> four from Europe (9%),<sup>16, 19, 24, 25</sup> and seven from the Americas (1%).<sup>14, 15, 17, 18, 20-22</sup> The mean age of study participants ranged from 43 to 83 years, and the mean study duration ranged from two to 35 years across studies. The included studies were generally of good to very good quality (Supplementary Table 1). There was variation in the incidence rates for dementia between populations (Supplementary Table 2).

Compared with not having diabetes, diabetes was significantly associated with approximately 60% increased risk of any dementia in both sexes; the multiple-adjusted pooled RR (95% CI) for any dementia associated with diabetes was 1.68 (1.64-1.71) in women and 1.61 (1.42-1.83) in men (Figures 1 and 2). There was moderate heterogeneity between studies in both women ( $I^2=40\%$ ;  $p=0.065$ ) and men ( $I^2=48\%$ ,  $p=0.048$ ). The size of the associations in women and men remained robust after excluding data, in turn, from the two large Asian cohorts (Supplementary Figure 2). Results from the age-adjusted analyses were not materially different: RR 1.58 (1.41–1.78) in women and 1.65 (1.46–1.87) in men. ~~(Supplementary Figures 3 and 4).~~ Restricting the analysis to studies that used higher quality research criteria to diagnose dementia had little effect on the summary estimates: 1.65 (1.42–1.91) in women and 1.49 (1.19–1.87) in men.

Diabetes was associated with a significantly increased risk of vascular dementia in both women and men; the multiple-adjusted pooled RR (95% CI) was 2.34 (1.86-2.94) in women and 1.73 (1.61-1.85) in men (Figures 1 and 2). Between-study heterogeneity was moderate for women ( $I^2=34\%$ ,  $p=0.14$ ), and was absent for men ( $I^2=0\%$ ,  $p=0.86$ ). Excluding data from either of the large Asian cohorts had no discernible impact on the results (Supplementary Figure 2). The age-adjusted estimates were 2.23 (1.72-2.90) in women, and 2.02 (1.90–2.16) in men. The summary estimates from those studies that used the higher quality research criteria for the diagnosis of dementia did not differ appreciably from the multiple-adjusted estimates: 2.43 (1.67–3.54) and 1.86 (1.25–2.76).

Individuals with diabetes also had 50% increased risk of developing non-vascular dementia compared with unaffected people: the multiple-adjusted pooled RR (95% CI) was 1.53 (1.35-1.73) in women and 1.49 (1.31-1.69) in men (Figures 1 and 2). Between-study heterogeneity was low-moderate in both sexes ( $I^2=30\%$ ,  $p=0.16$  in women and  $19\%$ ,  $p=0.27$  in men). These estimates were largely unaffected after exclusion of data from the two largest studies (Supplementary Figure 2). The age-adjusted estimates were weaker in both women and men: 1.44 (1.26 -1.65) and 1.34 (1.05-1.70), respectively. Restricting to studies that used research criteria for the diagnosis of dementia did not materially affect the summary estimates: 1.47 (1.20–1.81) in women and 1.34 (0.99–1.80) in men.

Diabetes conferred a significantly greater excess risk of developing dementia in women, but this was confined to vascular dementia (Figure 3). Women with diabetes had 19% (8-30%;  $p < 0.001$ ) greater excess risk of vascular dementia compared with men with diabetes, with no evidence of significant between-study heterogeneity ( $I^2=0\%$ ;  $p = 0.58$ ). This effect remained

following exclusion of data from the Korean study (RRR 1.18: 1.07–1.30) and the Taiwanese study, although it was then no longer statistically significant: RRR 1.33 (0.94–1.88) (Supplementary Figure 23). In the age-adjusted analysis, there was no significant sex difference in the association between diabetes and vascular dementia (RRR 1.10 [0.84–1.45],  $p=0.49$ ); ~~Supplementary Figure 6~~. For non-vascular dementia there was no evidence of a sex difference in the effect of diabetes from either the multiple-adjusted estimate (Figure 3) or the age-adjusted estimate (~~Supplementary Figure 4~~ RRR 1.05 [0.81–1.36]). The results did not change appreciably after excluding data from the Taiwanese or Korean studies (Supplementary Figure 23). Restricting the analysis to those studies that used the research criteria for the diagnosis of dementia produced a similar pattern of results although the sex difference with vascular dementia was no longer statistically significant (RRR 1.24 [0.73–2.11]).

Given the substantial variation in background rates of dementia and its major subtypes across the studies we examined what impact such heterogeneity may have had on the RRR estimate through meta-regression analysis. ~~As shown in Supplementary Figure 5, the~~ overall estimate of the RRR was robust to between study differences in diabetes incident rates as there was no significant evidence that differences in background rates materially influenced the RRR estimate ~~for either vascular dementia ( $p_{\text{for heterogeneity}}=0.22$ ) or non-vascular dementia ( $p_{\text{for heterogeneity}}=0.30$ )~~.

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## DISCUSSION

This pooled analysis of 14 studies combined largely unpublished data from more than 2.3 million individuals and information on more than 102,000 incident cases of dementia—more

than seven times the amount of information as in previous reviews of the same topic.<sup>4, 10, 11</sup>

Our findings offer support for a role of diabetes in the etiology of dementia, although the magnitude of the relationship differs according to subtype Overall, diabetes was associated with about a 60% increased risk of all-cause dementia and 40% risk of non-vascular dementia in both women and men, independent of important confounders. For vascular dementia, the association was stronger with evidence of a stronger effect in women than in men. Compared with people with no diabetes, after adjusting for possible confounders, women with diabetes had 120% greater risk of developing vascular dementia compared with 70% greater risk in men, which equated to an 18% significantly greater excess risk in women with diabetes compared with similarly affected men. These results were largely robust to the exclusion of data from two large cohorts that together comprised 96% of all incident cases of dementia.<sup>6, 12</sup>

The recorded excess relative risk of vascular dementia in women might be an artifact of the data driven by higher absolute rates for incident dementia in men than in women in the background population. If this were true, then the relative effect of diabetes on incident dementia would be greater in women than in men in populations in which the absolute incident rate is higher in men than in women, but should converge when the rates are similar between the sexes. However, our present findings show evidence to the contrary, with a trend towards higher incident rate ratios (indicating a greater excess risk in women than men) in studies in which the background incident rates for dementia were higher in women than in men.

Previous reviews of the association between diabetes and risk of dementia reported slightly larger estimates but still compatible to those presented here.<sup>4, 10, 11</sup> Moreover, as these reviews were reliant on published data they were largely unable to examine the effect of diabetes on dementia subtypes, the impact of confounding, or to perform sex-specific comparisons. In contrast, by sourcing previously unpublished study-level estimates, we were largely able to overcome these limitations. Moreover, by standardizing the level of adjustment for other major vascular risk factors across studies (as far as possible) we not only lessened the possible effect of residual confounding on study estimates, but we could also examine whether adjustment had a similar effect on the age-adjusted estimates for women and men. Our findings indicated that adjustment for other vascular risk factors on the association between diabetes and risk of vascular dementia had opposing effects in women and men: in women, adjustment tended to strengthen the association (by roughly 7%) whereas in men the association was somewhat weakened (by 14%) – which would explain the lack of an observed sex difference in the risk of diabetes for vascular dementia in the age-adjusted estimate.

While several processes are thought to promote the onset of dementia in individuals with diabetes, the biological basis of this relationship is still uncertain. Findings from a recent study that examined the genetic susceptibility to type 2 diabetes and risk of late-onset AD have shown that genotype risk scores for diabetes were not associated with increased risk of late-onset AD.<sup>26</sup> Therefore, even though we attempted to control for confounding, it is probable that the observed association between diabetes and non-vascular dementia is non-causal and possibly driven by other disease processes or known (and unknown) risk factors that are common to both diabetes and non-vascular dementia. But, both the size of



the association, and the fact that diabetes is a known risk factor for micro- and macrovascular complications—including CHD and stroke, would suggest that the relationship between diabetes and vascular dementia is robust and not solely driven by confounding.

Studies in support of a biological relationship between diabetes and vascular and non-vascular dementia, suggest a multifactorial pathogenesis involving insulin metabolism, hyperglycemic toxicity, chronic inflammatory processes and vascular changes.<sup>27, 28</sup> Insulin resistance is thought to promote atherosclerosis, change cerebral energy metabolism, and to lead to vascular-related cognitive impairment and dementia.<sup>27</sup> Oxidative stress due to chronic hyperglycemia can also lead to vascular changes in the nervous system, and an accumulation of advanced glycation end-products that are found in AD.<sup>28</sup> Conversely, severe hypoglycaemia, which in most cases is driven by insulin or sulfonylurea treatment of diabetes, is associated with cognitive impairment by precipitating neuronal death and increased production of coagulation factors.<sup>27</sup> Type 2 diabetes is also associated with an increased expression of interleukin-6 (IL-6) in the central nervous system, causing inflammation of the brain and in conjunction with oxidative stress is implicated in the pathogenesis of AD.<sup>27</sup> Two prospective neuropathological cohort studies suggested that diabetes may lower the threshold for the amount of amyloid required for development of AD by inducing adverse microvascular changes—small vessel infarcts—in the brain.<sup>28,29</sup> There is now growing evidence to suggest that dementia subtypes are more heterogeneous pathologically than previously thought, and underlying vascular changes play a role in both vascular and non-vascular dementia.<sup>3</sup>

The present analyses provide further support for the hypothesis that the adverse consequences of diabetes on vascular risk are stronger in women than in men.<sup>7-9</sup> While a sex disparity in the management and treatment of diabetes, most often to the detriment of women, may be involved, accruing evidence suggests that real biological differences between women and men underpin the excess risk of diabetes-related vascular risk in women. For example, exposure to endogenous estradiol in women may also play a role; a recent study among post-menopausal women found that higher levels of endogenous estradiol, especially in women with diabetes, conferred a greater risk of dementia.<sup>30</sup> There is also some evidence from autopsy studies to suggest that the greater diabetes-related excess risk of vascular dementia observed in women may be mediated by greater neurological microvascular damage: based on neuropathological assessment the Adult Changes in Thought Study reported two patterns of cerebral injury associated with dementia in individuals with and without diabetes. In those without diabetes, dementia was associated with higher amyloid-B peptide while in individuals with diabetes, dementia was characterised by greater microvascular infarcts and neuroinflammation<sup>31</sup>. However, whether the latter was more pronounced in women than in men was not examined and requires further investigation by future studies that are adequately powered to detect sex differences.

Limitations of our study include the differences across studies in study design and duration, endpoint definition, and ascertainment of diabetes (which was either measured or based on self-report depending on the study). We were also unable to include data from 14 eligible cohorts with 2,300 incident cases of dementia. However, given that the current analyses are based on more than 100,000 incident cases it is unlikely that their omission had a profound

impact on the results. It should be noted however, that more than 96% of the cases were derived from two large studies; reassuringly however, exclusion of either study did not materially alter the pattern of the results (although in some instances the associations were not statistically significant). It should be noted however, that the heterogeneity in the method of diagnosis of dementia and its subtypes is a significant (and unquantifiable) limitation of this analysis. For example, ascertainment of dementia from the two large Asian cohorts was reliant on diagnoses obtained from administrative databases that may be particularly susceptible to detection bias or case reporting, (supplementary reference 16)<sup>32</sup> whereas in other, much smaller studies, a diagnosis of dementia was based on clinical examination by two or more clinicians<sup>25</sup>. We also did not examine the association between duration of diabetes or glycaemic control and the risk for dementia, nor did we evaluate the association between diabetes and cognitive functioning. The diagnosis of vascular dementia in epidemiological studies, and its overlap with AD and other forms of dementia, without neuropathological validation is also a significant limitation and may have overestimated the impact of diabetes for dementia subtypes. While we used accepted criteria to distinguish between Alzheimer’s disease and vascular dementia, there is increasing recognition that dementia has a mixed pathophysiology (Supplementary references 17,18) by 23<sup>34</sup>. At the present, no standardised thresholds by which to categorise mixed dementia exist, and was not examined within the individual studies, hence, we were unable to examine sex differences in the diabetes-related risk of mixed dementia. Misclassification of dementia status – which may have occurred differentially in women and men – will have introduced bias, the extent (and direction) of which remains unknown. We also did not have information on duration of diabetes status and level of glycemic control either of which may

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have significantly interacted with risk of dementia (either to a similar or different extent in women and men).

Future prospective studies, with extensive phenotypic and genetic data on risk factors common to both diabetes and subtypes of dementia, are needed to examine whether these relationships are causal. Moreover, our finding of a greater diabetes-related risk of vascular dementia in women than in men contributes to the growing evidence base that diabetes confers a proportionally greater vascular hazard in women than in men.

#### **GUARANTOR'S STATEMENT**

Professor Rachel Huxley is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

#### **DECLARATION OF INTERESTS**

No conflict of interest for any author.

#### **AUTHOR CONTRIBUTIONS**

SC performed the literature review, obtained the data, interpreted the data and drafted the manuscript. SAEP conducted the analyses, interpreted the data and drafted the manuscript. MW oversaw the statistical analysis, interpreted the data and provided critical revision of the manuscript. SMA, GDB, NB, AB, ARB, PKC, MH, LBH, KMH, YK, EBL, CYL, TN, TO, RP, TCR, SS, BHS, RW, and WX provided the data and provided critical revision of the manuscript. RRH conceived the idea, interpreted the data, drafted the manuscript and provided critical

revision of the manuscript. RRH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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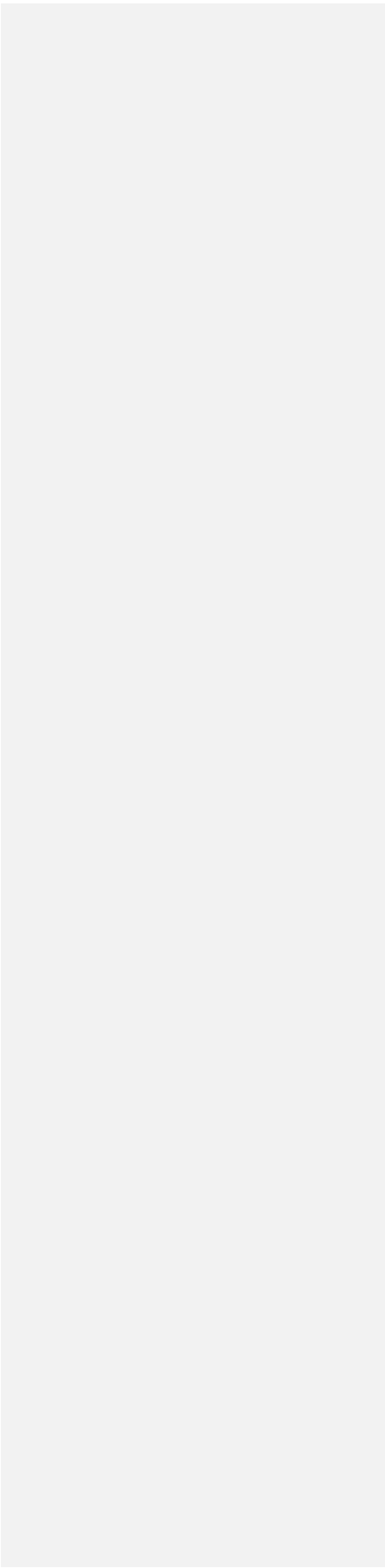
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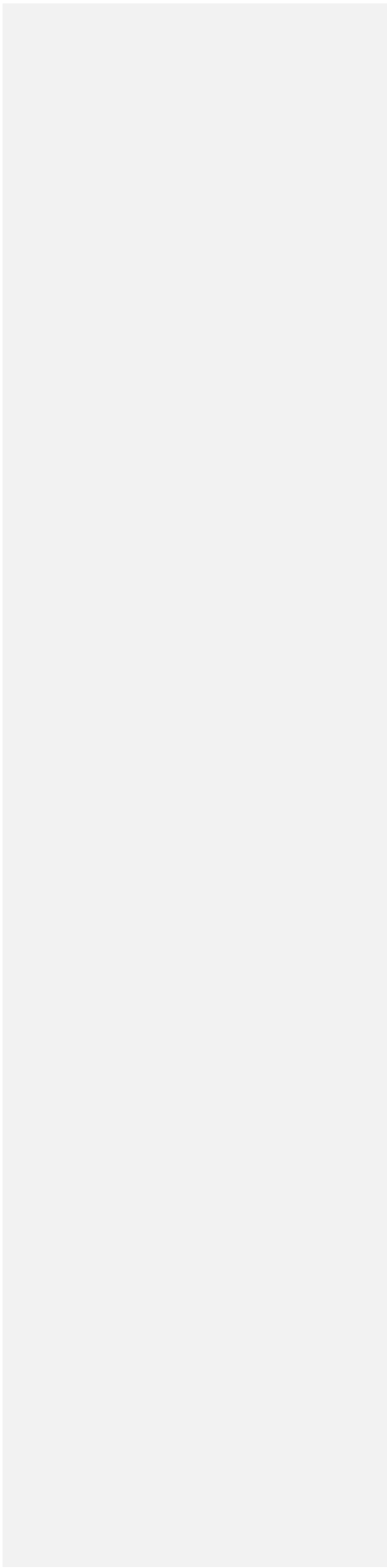
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**FIGURE LEGEND**

**Figure 1: Multiple-adjusted relative risk for any dementia, vascular dementia and non-vascular dementia in women, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RR=relative risk; CI=confidence interval.

**Figure 2: Multiple-adjusted relative risk for any dementia, vascular dementia and non-vascular dementia in men, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RR=relative risk; CI=confidence interval.

**Figure 3: Multiple-adjusted women to men ratio of relative risks for any dementia, vascular dementia and non-vascular dementia, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RRR= women to men ratio of relative risk; CI=confidence interval.

Table 1: Characteristics of included studies

Cohort	Country	Baseline study (years)	Mean FU (years)	Age range (years)	N (% w)	N diabetes (% w)	N dementia (% w)	N VaD (% w)	N non-VaD (% w)	Ascertainment of diabetes	Ascertainment of dementia	Maximum adjustment available
ACT Study <sup>18</sup>	US	1994-96	7	65+	2067 (59)	232 (52)	524 (62)	67 (61)	457 (62)	Measured	Cognitive Abilities Screening Instrument, DSM, NINCDS/ADRDA	Age, sbp, smoking, bmi
ARIC <sup>15</sup>	US	1990-92	14	46-70	11151 (57)	1445 (55)	203 (57)	NA	NA	Measured or SR	ICD-9 codes	Age, race, sbp, smoking, bmi, tc
CCMS <sup>20</sup>	US	1995	5	65+	3260 (58)	343 (53)	141 (71)	37 (65)	104 (73)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, hypertension, bmi, high cholesterol
English and Scottish Health surveys <sup>16</sup>	UK	1998-08	8	16-102	154844 (52)	12267 (48)	1242 (54)	NA	NA	SR	ICD-9, ICD-10 codes	Age, sbp, smoking, bmi, tc
Framingham Study <sup>14</sup>	US	1976-78	13	NR	2609 (56)	363 (43)	234 (61)	51 (61)	183 (61)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc
Hisayama Study <sup>23</sup>	Japan	1985-88	15	60+	1017 (57)	150 (55)	232 (66)	65 (51)	167 (72)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc

Cohort	Country	Baseline study (years)	Mean FU (years)	Age range (years)	N (% w)	N diabetes (% w)	N dementia (% w)	N VaD (% w)	N non-VaD (% w)	Ascertainment of diabetes	Ascertainment of dementia	Maximum adjustment available
Kame Project <sup>17</sup>	US	1992-1994	6	65+	1709 (55)	290 (44)	140 (59)	45 (58)	112 (63)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi
Kungsholmen Project <sup>25</sup>	Sweden	1987-89	9	75+	1301 (75)	104 (75)	350 (81)	49 (71)	301 (83)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi
MHAS <sup>22</sup>	Mexico	2001-03	3	60 +	5398 (54)	749 (61)	306 (60)	54 (63)	230 (61)	SR	CCCE, IQCODE	Age, hypertension, smoking, obesity
NHI, Taiwan <sup>12</sup>	Taiwan	2000-08	9	NR	1229747 (52)	614876 (52)	95087 (57)	8300 (52)	86757 (57)	Measured	ICD-9 codes	Age, insurance premium, region, urbanization cbvd, cvd, hypertension, hyperlipidemia
NHIC, Korea <sup>6</sup>	Korea	1992-95	14	40-95	848505 (42)	51611 (35)	2914 (55)	516 (47)	1669 (57)	Measured	DSM and medical examination	Age, alcohol
Norwegian Counties Study <sup>24</sup>	Norway	1974-78	35	35-50	46231 (51)	613 (34)	460 (53)	NA	NA	Measured or SR	ICD-9 codes	Age, sbp, smoking, bmi, tc
OCTO-Twin Study <sup>19, 21</sup>	Sweden	1991-99	9	80+	702 (67)	122 (67)	225 (70)	57 (58)	163 (73)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc
SALSA Study <sup>21</sup>	US	1998-99	10	60+	1789 (58)	797 (56)	116 (66)	12 (50)	90 (71)	Measured or SR	DSM, NINCDS/ADRDA,	Age, sbp, smoking, bmi, tc

NINDS-AIREN

Study abbreviations: %w; percent women; ACT, Adult Changes in Thought; ARIC, Atherosclerosis Risk in Communities Study; CCMS, Cache County Memory Study; MHAS, Mexican Health and Aging Study; NHI, National Health Insurance; NHIC, National Health Insurance Corporation; OCTO, Origins of Variance in the Old-Old; SALSA, Sacramento Area Latino Study on Aging.

Abbreviations: BMI, body mass index; CCCE, Cross-Cultural Cognitive Examination; cbvd, cerebrovascular disease; cvd, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Disease; IQCODE Informant Questionnaire on COgnitive Decline in the Elderly; NA, not available; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria; sbp, systolic blood pressure; tc, total cholesterol, VaD, Vascular Dementia; SR, self-report diabetes; UK, United Kingdom; US, United States of America

**Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia**

Short running title: Sex differences in diabetes-related risk of dementia

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**ABSTRACT**

**Objective:** Type 2 diabetes confers a greater excess risk of cardiovascular disease in women than in men. Diabetes is also a risk factor for dementia but whether the association is similar in women and men remains unknown. We performed a meta-analysis of unpublished data to estimate the sex-specific relationship between diabetes with incident dementia.

**Research Design and Methods:** A systematic search identified studies published prior to November 2014 that had reported on the prospective association between diabetes and dementia. Study authors contributed unpublished sex-specific relative risks (RR) and 95% confidence intervals (95% CI) on the association between diabetes and all dementia and its subtypes. Sex-specific RRs and the women-to-men ratio of RRs (RRRs) were pooled using random-effects meta-analyses.

**Results:** Study-level data from 14 studies, 2,310,330 individuals and 102 174 dementia cases were included. In multiple-adjusted analyses, diabetes was associated with 60% increased risk of any dementia in both sexes: pooled RR (95% CI) 1.62 (1.45-1.80) in women, and 1.58 (1.38-1.81) in men, respectively. The diabetes-associated RRs (95% CI) for vascular dementia were 2.34 (1.86-2.94) in women and 1.73 (1.61-1.85) in men, and for non-vascular dementia were 1.53 (1.35-1.73) in women and 1.49 (1.31-1.69) in men. Overall, women with diabetes had 19% greater risk of developing vascular dementia than men: multiple-adjusted RRR 1.19 (1.08-1.30)  $p < 0.001$ .

**Conclusions:** Individuals with type 2 diabetes are at approximately 60% greater risk of developing dementia compared with those without diabetes. For vascular, but not for non-vascular dementia, the additional risk is greater in women.

Dementia is a multi-faceted syndrome that lays claim to a growing burden of global disease: the most recent estimates suggest that there are approximately 44 million affected individuals worldwide and a further 7.7 million new cases annually.<sup>1, 2</sup> Underpinned by a shifting demographic and associated epidemiological profile worldwide, the prevalence of dementia is forecast to nearly double by 2030, and to triple by 2050, and is set to create a significant economic, social and public health burden particularly in resource-poor countries.<sup>1, 2</sup>

Non-vascular dementia, which mainly constitutes Alzheimer's disease (AD), and vascular dementia are the two most common forms of dementia, accounting for about 70% (25 million) and 20% (7 million) of all dementia cases, respectively.<sup>2</sup> Lifestyle risk factors including type 2 diabetes, cigarette smoking, and obesity are associated with an increased risk of developing both vascular dementia and non-vascular dementia in later life.<sup>3</sup> For example, a review that included information on approximately 15,000 cases of dementia, found that, compared to non-affected individuals, those with diabetes had roughly 70% greater risk of developing dementia.<sup>4</sup>

While of value, this review has some important limitations<sup>4</sup>: over 73% of dementia cases were derived from two large Asian cohorts,<sup>5, 6</sup> and the influence of these studies on the overall summary estimates was not examined. Moreover, information on dementia subtypes was not universally available, including the single study that provided information on more than 50% of all dementia cases.<sup>5</sup> Finally, as the analyses were not sex-specific it was not possible to determine whether the magnitude of the association between diabetes and incident dementia and its main subtypes differed in women and men. This is of interest

given the substantial amount of evidence suggesting that diabetes confers a significantly greater additional vascular hazard in women compared with men which potentially has ramifications for the clinical management of diabetes and vascular disease in women.<sup>7-9</sup>

To overcome the substantial methodological limitations of past reviews, we requested individual study investigators to contribute unpublished results to a pooled analysis. In line with the current evidence base which suggests that diabetes poses more of a vascular hazard in women compared with men, our hypothesis was that diabetes confers a greater excess risk of vascular dementia in women than in men but that the impact of diabetes on risk of non-vascular dementia is similar between the sexes.

## RESEARCH DESIGN AND METHODS

### *Search strategy and selection criteria*

We used PubMed MEDLINE ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)) and OVID MEDLINE for the period from January, 2011 to November, 2014 to identify studies that had reported on the association between diabetes and dementia in men and women from a general population. The search strategy combined the following text terms and MeSH: 'dementia', 'vascular dementia', 'delirium', 'cognitive disorders', 'amnesic disorders', 'frontotemporal dementia', multi-infarct dementia', 'Alzheimer disease', 'Lewy body', 'type 2 diabetes mellitus', 'diabetes mellitus', 'DM', 'diabetes complications', 'blood glucose', 'impaired glucose tolerance', 'glycosylated hemoglobin', and 'prediabetes'. Studies prior to 2011 were identified from previous systematic reviews.<sup>4, 10, 11</sup> Data from randomized trials were excluded due to the non-generalizable nature of trials to the general population. Two authors (SAEP and SC) conducted the literature search. Uncertainties regarding the identification of studies were

discussed and resolved by mutual consent. Since most studies did not publish estimates of relative risk separately for men and women or for dementia subtypes, and varied by which factors were included in adjusted models, we contacted authors of all the selected studies and asked them to provide additional results adjusted, where possible, for the same set of confounders: blood pressure, cigarette smoking, body mass index and total cholesterol. On a specifically designed form, contributing authors provided summary results for the age- and multiple-adjusted relative risks (RRs) and 95% confidence intervals (CIs) for any dementia, and if available, for vascular dementia and non-vascular dementia segregated by sex.

#### *Data extraction and statistical analysis*

The primary endpoints were incident all-cause dementia, vascular dementia, and non-vascular dementia (as defined by the study investigators: see Supplementary Table 1). The primary metrics were the pooled multiple-adjusted RRs for dementia associated with diabetes and the women-to-men ratio of the RRs (RRR). Covariates that were included in the multiple-adjusted model were reported differently between studies and are shown in Table 1. Age-adjusted estimates were used in a secondary analysis. From each study, we obtained the previously unpublished sex-specific RRs with accompanying 95% CIs for individuals with versus without diabetes. We also requested information on person-years of follow-up to calculate sex-specific incidence rates in individuals with and without diabetes. We log-transformed these RRs and pooled them across studies using random effects meta-analysis with inverse variance weighting, and then exponentiated these values to obtain the pooled RR separately for women and men. We used similar methods to pool women-to-men ratio of RRs. For each study, we obtained the standard error of the log RRR by taking the square root of the sum of the variance of the two sex-specific log RRs. We used the  $I^2$  statistic to

estimate the percentage of variability across studies due to between-study heterogeneity. In sensitivity analyses, we excluded estimates from two large cohort studies from Taiwan and Korea which had a large influence on the summary estimates.<sup>6, 12</sup> We also examined whether restricting the analysis to those studies that used higher quality research criteria for dementia diagnosis (e.g. the Cross cultural Cognitive Examination, National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association criteria) affected the main results. We explored whether the background rate of dementia in the study population influenced the sex-specific associations by meta-regression analyses of the log RRR versus the difference in incidence rate between women with and without diabetes minus the equivalent estimate in men (i.e. the difference of the difference). We assessed the methodological quality of the studies using the Newcastle-Ottawa Scale (Supplementary methods).<sup>13</sup> All analyses were performed using Stata version 12.0.

## RESULTS

The systematic search identified 1495 unique articles that were subsequently examined on title and abstract (Supplementary Figure 1). Overall, 1425 articles were excluded for one or more reasons including lack of primary data, single-sex population, animal study, non-prospective study design, and randomized trial of a high-risk population. Of the remaining articles, 70 articles qualified for full-text evaluation. Of these, 28 studies had relevant data on the relationship between diabetes and risk of dementia and the authors were contacted and asked to contribute additional estimates to those in the published reports. Authors from 13 studies (response 48%) contributed unpublished summary data,<sup>12, 14-25</sup> and for one study we extracted the necessary data from its published report.<sup>6</sup> The 14 non-contributing



studies comprised 30,900 individuals and 2,300 cases of dementia (Supplementary references) and the baseline characteristics are described in Table 1. Overall, data were available on 2,310,330 individuals (48% women) and 102,174 incident cases of dementia, including 9,253 cases of vascular dementia (52% women) and 90,233 cases of non-vascular dementia (58% women). Three cohorts were from Asia (90% of the individuals),<sup>6, 12, 23</sup> four from Europe (9%),<sup>16, 19, 24, 25</sup> and seven from the Americas (1%).<sup>14, 15, 17, 18, 20-22</sup> The mean age of study participants ranged from 43 to 83 years, and the mean study duration ranged from two to 35 years across studies. The included studies were generally of good to very good quality (Supplementary Table 1). There was variation in the incidence rates for dementia between populations (Supplementary Table 2).

Compared with not having diabetes, diabetes was significantly associated with approximately 60% increased risk of any dementia in both sexes; the multiple-adjusted pooled RR (95% CI) for any dementia associated with diabetes was 1.68 (1.64-1.71) in women and 1.61 (1.42-1.83) in men (Figures 1 and 2). There was moderate heterogeneity between studies in both women ( $I^2=40\%$ ;  $p=0.065$ ) and men ( $I^2=48\%$ ,  $p=0.048$ ). The size of the associations in women and men remained robust after excluding data, in turn, from the two large Asian cohorts (Supplementary Figure 2). Results from the age-adjusted analyses were not materially different: RR 1.58 (1.41–1.78) in women and 1.65 (1.46–1.87) in men. Restricting the analysis to studies that used higher quality research criteria to diagnose dementia had little effect on the summary estimates: 1.65 (1.42–1.91) in women and 1.49 (1.19–1.87) in men.

Diabetes was associated with a significantly increased risk of vascular dementia in both women and men; the multiple-adjusted pooled RR (95% CI) was 2.34 (1.86-2.94) in women and 1.73 (1.61-1.85) in men (Figures 1 and 2). Between-study heterogeneity was moderate for women ( $I^2=34\%$ ,  $p=0.14$ ), and was absent for men ( $I^2=0\%$ ,  $p=0.86$ ). Excluding data from either of the large Asian cohorts had no discernible impact on the results (Supplementary Figure 2). The age-adjusted estimates were 2.23 (1.72-2.90) in women, and 2.02 (1.90–2.16) in men. The summary estimates from those studies that used the higher quality research criteria for the diagnosis of dementia did not differ appreciably from the multiple-adjusted estimates: 2.43 (1.67–3.54) and 1.86 (1.25–2.76).

Individuals with diabetes also had 50% increased risk of developing non-vascular dementia compared with unaffected people: the multiple-adjusted pooled RR (95% CI) was 1.53 (1.35-1.73) in women and 1.49 (1.31-1.69) in men (Figures 1 and 2). Between-study heterogeneity was low-moderate in both sexes ( $I^2=30\%$ ,  $p=0.16$  in women and  $19\%$ ,  $p=0.27$  in men). These estimates were largely unaffected after exclusion of data from the two largest studies (Supplementary Figure 2). The age-adjusted estimates were weaker in both women and men: 1.44 (1.26 -1.65) and 1.34 (1.05-1.70), respectively. Restricting to studies that used research criteria for the diagnosis of dementia did not materially affect the summary estimates: 1.47 (1.20–1.81) in women and 1.34 (0.99–1.80) in men.

Diabetes conferred a significantly greater excess risk of developing dementia in women, but this was confined to vascular dementia (Figure 3). Women with diabetes had 19% (8-30%;  $p<0.001$ ) greater excess risk of vascular dementia compared with men with diabetes, with no evidence of significant between-study heterogeneity ( $I^2=0\%$ ;  $p=0.58$ ). This effect remained

following exclusion of data from the Korean study (RRR 1.18: 1.07–1.30) and the Taiwanese study, although it was then no longer statistically significant: RRR 1.33 (0.94-1.88) (Supplementary Figure 2). In the age-adjusted analysis, there was no significant sex difference in the association between diabetes and vascular dementia (RRR 1.10 [0.84-1.45],  $p=0.49$ ). For non-vascular dementia there was no evidence of a sex difference in the effect of diabetes from either the multiple-adjusted estimate (Figure 3) or the age-adjusted estimate (RRR 1.05 [0.81-1.36]). The results did not change appreciably after excluding data from the Taiwanese or Korean studies (Supplementary Figure 2). Restricting the analysis to those studies that used the research criteria for the diagnosis of dementia produced a similar pattern of results although the sex difference with vascular dementia was no longer statistically significant (RRR 1.24 [0.73-2.11]).

Given the substantial variation in background rates of dementia and its major subtypes across the studies we examined what impact such heterogeneity may have had on the RRR estimate through meta-regression analysis. The overall estimate of the RRR was robust to between study differences in diabetes incident rates as there was no significant evidence that differences in background rates materially influenced the RRR estimate for either vascular dementia ( $p_{\text{for heterogeneity}} = 0.22$ ) or non-vascular dementia ( $p_{\text{for heterogeneity}} = 0.30$ )

## DISCUSSION

This pooled analysis of 14 studies combined largely unpublished data from more than 2.3 million individuals and information on more than 102,000 incident cases of dementia—more than seven times the amount of information as in previous reviews of the same topic.<sup>4, 10, 11</sup> Our findings offer support for a role of diabetes in the etiology of dementia, although the

magnitude of the relationship differs according to subtype Overall, diabetes was associated with about a 60% increased risk of all-cause dementia and 40% risk of non-vascular dementia in both women and men, independent of important confounders. For vascular dementia, the association was stronger with evidence of a stronger effect in women than in men. Compared with people with no diabetes, after adjusting for possible confounders, women with diabetes had 120% greater risk of developing vascular dementia compared with 70% greater risk in men, which equated to an 18% significantly greater excess risk in women with diabetes compared with similarly affected men. These results were largely robust to the exclusion of data from two large cohorts that together comprised 96% of all incident cases of dementia.<sup>6, 12</sup>

The recorded excess relative risk of vascular dementia in women might be an artifact of the data driven by higher absolute rates for incident dementia in men than in women in the background population. If this were true, then the relative effect of diabetes on incident dementia would be greater in women than in men in populations in which the absolute incident rate is higher in men than in women, but should converge when the rates are similar between the sexes. However, our present findings show evidence to the contrary, with a trend towards higher incident rate ratios (indicating a greater excess risk in women than men) in studies in which the background incident rates for dementia were higher in women than in men.

Previous reviews of the association between diabetes and risk of dementia reported slightly larger estimates but still compatible to those presented here.<sup>4, 10, 11</sup> Moreover, as these reviews were reliant on published data they were largely unable to examine the effect of

diabetes on dementia subtypes, the impact of confounding, or to perform sex-specific comparisons. In contrast, by sourcing previously unpublished study-level estimates, we were largely able to overcome these limitations. Moreover, by standardizing the level of adjustment for other major vascular risk factors across studies (as far as possible) we not only lessened the possible effect of residual confounding on study estimates, but we could also examine whether adjustment had a similar effect on the age-adjusted estimates for women and men. Our findings indicated that adjustment for other vascular risk factors on the association between diabetes and risk of vascular dementia had opposing effects in women and men: in women, adjustment tended to strengthen the association (by roughly 7%) whereas in men the association was somewhat weakened (by 14%) – which would explain the lack of an observed sex difference in the risk of diabetes for vascular dementia in the age-adjusted estimate.

While several processes are thought to promote the onset of dementia in individuals with diabetes, the biological basis of this relationship is still uncertain. Findings from a recent study that examined the genetic susceptibility to type 2 diabetes and risk of late-onset AD have shown that genotype risk scores for diabetes were not associated with increased risk of late-onset AD.<sup>26</sup> Therefore, even though we attempted to control for confounding, it is probable that the observed association between diabetes and non-vascular dementia is non-causal and possibly driven by other disease processes or known (and unknown) risk factors that are common to both diabetes and non-vascular dementia. But, both the size of the association, and the fact that diabetes is a known risk factor for micro- and macrovascular complications—including CHD and stroke, would suggest that the relationship between diabetes and vascular dementia is robust and not solely driven by confounding.

Studies in support of a biological relationship between diabetes and vascular and non-vascular dementia, suggest a multifactorial pathogenesis involving insulin metabolism, hyperglycemic toxicity, chronic inflammatory processes and vascular changes.<sup>27, 28</sup> Insulin resistance is thought to promote atherosclerosis, change cerebral energy metabolism, and to lead to vascular-related cognitive impairment and dementia.<sup>27</sup> Oxidative stress due to chronic hyperglycemia can also lead to vascular changes in the nervous system, and an accumulation of advanced glycation end-products that are found in AD.<sup>28</sup> Conversely, severe hypoglycaemia, which in most cases is driven by insulin or sulfonylurea treatment of diabetes, is associated with cognitive impairment by precipitating neuronal death and increased production of coagulation factors.<sup>27</sup> Type 2 diabetes is also associated with an increased expression of interleukin-6 (IL-6) in the central nervous system, causing inflammation of the brain and in conjunction with oxidative stress is implicated in the pathogenesis of AD.<sup>27</sup> Two prospective neuropathological cohort studies suggested that diabetes may lower the threshold for the amount of amyloid required for development of AD by inducing adverse microvascular changes—small vessel infarcts—in the brain.<sup>28,29</sup> There is now growing evidence to suggest that dementia subtypes are more heterogeneous pathologically than previously thought, and underlying vascular changes play a role in both vascular and non-vascular dementia.<sup>3</sup>

The present analyses provide further support for the hypothesis that the adverse consequences of diabetes on vascular risk are stronger in women than in men.<sup>7-9</sup> While a sex disparity in the management and treatment of diabetes, most often to the detriment of women, may be involved, accruing evidence suggests that real biological differences

between women and men underpin the excess risk of diabetes-related vascular risk in women. For example, exposure to endogenous estradiol in women may also play a role; a recent study among post-menopausal women found that higher levels of endogenous estradiol, especially in women with diabetes, conferred a greater risk of dementia.<sup>30</sup> There is also some evidence from autopsy studies to suggest that the greater diabetes-related excess risk of vascular dementia observed in women may be mediated by greater neurological microvascular damage: based on neuropathological assessment the Adult Changes in Thought Study reported two patterns of cerebral injury associated with dementia in individuals with and without diabetes. In those without diabetes, dementia was associated with higher amyloid-B peptide while in individuals with diabetes, dementia was characterised by greater microvascular infarcts and neuroinflammation (supplementary reference 15)<sup>31</sup>. However, whether the latter was more pronounced in women than in men was not examined and requires further investigation by future studies that are adequately powered to detect sex differences.

Limitations of our study include the differences across studies in study design and duration, endpoint definition, and ascertainment of diabetes (which was either measured or based on self-report depending on the study). We were also unable to include data from 14 eligible cohorts with 2,300 incident cases of dementia. However, given that the current analyses are based on more than 100,000 incident cases it is unlikely that their omission had a profound impact on the results. It should be noted however, that more than 96% of the cases were derived from two large studies; reassuringly however, exclusion of either study did not materially alter the pattern of the results (although in some instances the associations were not statistically significant). It should be noted however, that the heterogeneity in the

method of diagnosis of dementia and its subtypes is a significant (and unquantifiable) limitation of this analysis. For example, ascertainment of dementia from the two large Asian cohorts was reliant on diagnoses obtained from administrative databases that may be particularly susceptible to detection bias or case reporting, (supplementary reference 16) whereas in other, much smaller studies, a diagnosis of dementia was based on clinical examination by two or more clinicians<sup>25</sup>. We also did not examine the association between duration of diabetes or glycaemic control and the risk for dementia, nor did we evaluate the association between diabetes and cognitive functioning. The diagnosis of vascular dementia in epidemiological studies, and its overlap with AD and other forms of dementia, without neuropathological validation is also a significant limitation and may have overestimated the impact of diabetes for dementia subtypes. While we used accepted criteria to distinguish between Alzheimer's disease and vascular dementia, there is increasing recognition that dementia has a mixed pathophysiology (supplementary references 17, 18). At the present, no standardised thresholds by which to categorise mixed dementia exist, and was not examined within the individual studies, hence, we were unable to examine sex differences in the diabetes-related risk of mixed dementia. Misclassification of dementia status – which may have occurred differentially in women and men – will have introduced bias, the extent (and direction) of which remains unknown. We also did not have information on duration of diabetes status and level of glycemic control either of which may have significantly interacted with risk of dementia (either to a similar or different extent in women and men).

Future prospective studies, with extensive phenotypic and genetic data on risk factors common to both diabetes and subtypes of dementia, are needed to examine whether these relationships are causal. Moreover, our finding of a greater diabetes-related risk of vascular



dementia in women than in men contributes to the growing evidence base that diabetes confers a proportionally greater vascular hazard in women than in men.

#### **GUARANTOR'S STATEMENT**

Professor Rachel Huxley is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

#### **DECLARATION OF INTERESTS**

No conflict of interest for any author.

#### **AUTHOR CONTRIBUTIONS**

SC performed the literature review, obtained the data, interpreted the data and drafted the manuscript. SAEP conducted the analyses, interpreted the data and drafted the manuscript. MW oversaw the statistical analysis, interpreted the data and provided critical revision of the manuscript. SMA, GDB, NB, AB, ARB, PKC, MH, LBH, KMH, YK, EBL, CYL, TN, TO, RP, TCR, SS, BHS, RW, and WX provided the data and provided critical revision of the manuscript. RRH conceived the idea, interpreted the data, drafted the manuscript and provided critical revision of the manuscript. RRH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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#### **STUDY INVESTIGATORS**

Adult Changes in Thought Study (PK Crane, R Walker, E Larson); Atherosclerosis Risk in Communities Study (A Alonso); Cache County Memory Study (KM Hayden); English and Scottish Health Surveys (GD Batty, TC Russ); Framingham Study (A Beiser, S Seshadri); Hisayama Study (T Ohara, T Ninomiya, Y Kiyohara); Kame Project (AR Borenstein, EB Larson); Kungsholmen Project (WL Xu); Mexican Health and Aging Study (S Mejia-Arango); National Health Insurance (CY Li); Norwegian Counties Study (BH Strand); Origins of Variance in the Old-Old Twin Study (LB Hassing); Sacramento Area Latino Study on Aging (M Haan).

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**FIGURE LEGEND**

**Figure 1: Multiple-adjusted relative risk for any dementia, vascular dementia and non-vascular dementia in women, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RR=relative risk; CI=confidence interval.

**Figure 2: Multiple-adjusted relative risk for any dementia, vascular dementia and non-vascular dementia in men, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RR=relative risk; CI=confidence interval.

**Figure 3: Multiple-adjusted women to men ratio of relative risks for any dementia, vascular dementia and non-vascular dementia, comparing individuals with diabetes to those without diabetes.** Horizontal bars represent 95% confidence intervals. RRR= women to men ratio of relative risk; CI=confidence interval.



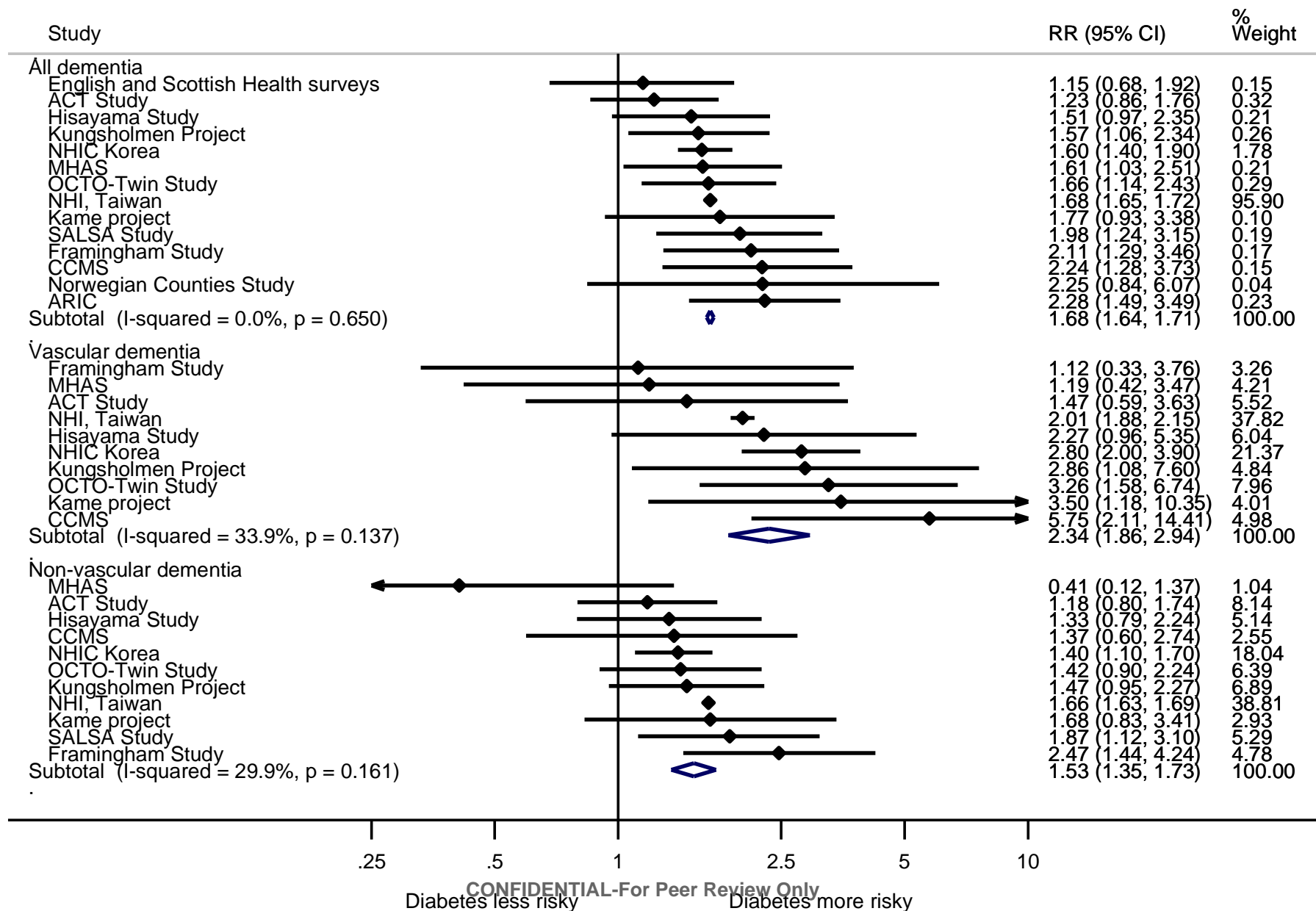
Table 1: Characteristics of included studies

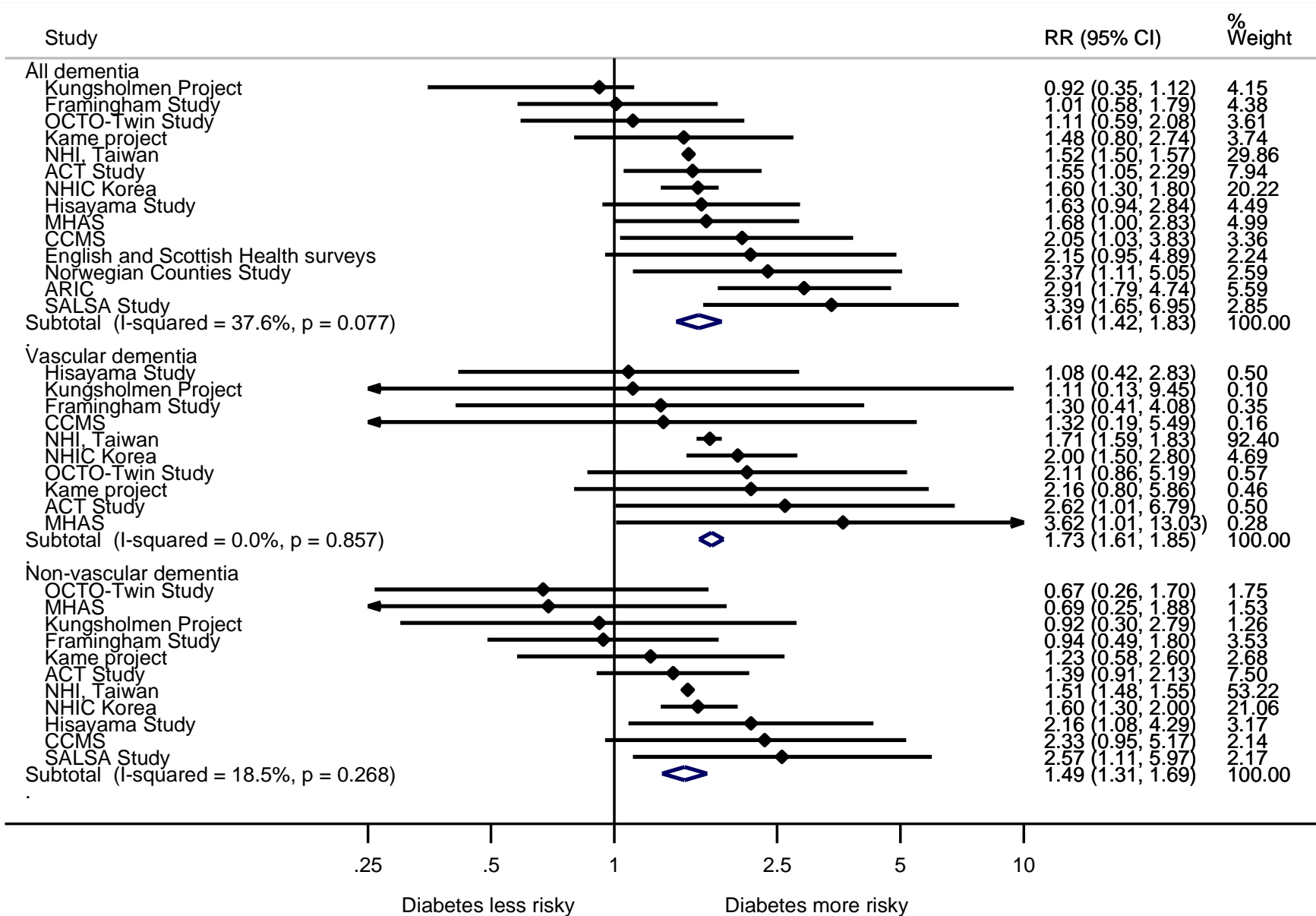
Cohort	Country	Baseline study (years)	Mean FU (years)	Age range (years)	N (% w)	N diabetes (% w)	N dementia (% w)	N VaD (% w)	N non-VaD (% w)	Ascertainment of diabetes	Ascertainment of dementia	Maximum adjustment available
ACT Study <sup>18</sup>	US	1994-96	7	65+	2067 (59)	232 (52)	524 (62)	67 (61)	457 (62)	Measured	Cognitive Abilities Screening Instrument, DSM, NINCDS/ADRDA	Age, sbp, smoking, bmi
ARIC <sup>15</sup>	US	1990-92	14	46-70	11151 (57)	1445 (55)	203 (57)	NA	NA	Measured or SR	ICD-9 codes	Age, race, sbp, smoking, bmi, tc
CCMS <sup>20</sup>	US	1995	5	65+	3260 (58)	343 (53)	141 (71)	37 (65)	104 (73)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, hypertension, bmi, high cholesterol
English and Scottish Health surveys <sup>16</sup>	UK	1998-08	8	16-102	154844 (52)	12267 (48)	1242 (54)	NA	NA	SR	ICD-9, ICD-10 codes	Age, sbp, smoking, bmi, tc
Framingham Study <sup>14</sup>	US	1976-78	13	NR	2609 (56)	363 (43)	234 (61)	51 (61)	183 (61)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc
Hisayama Study <sup>23</sup>	Japan	1985-88	15	60+	1017 (57)	150 (55)	232 (66)	65 (51)	167 (72)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc

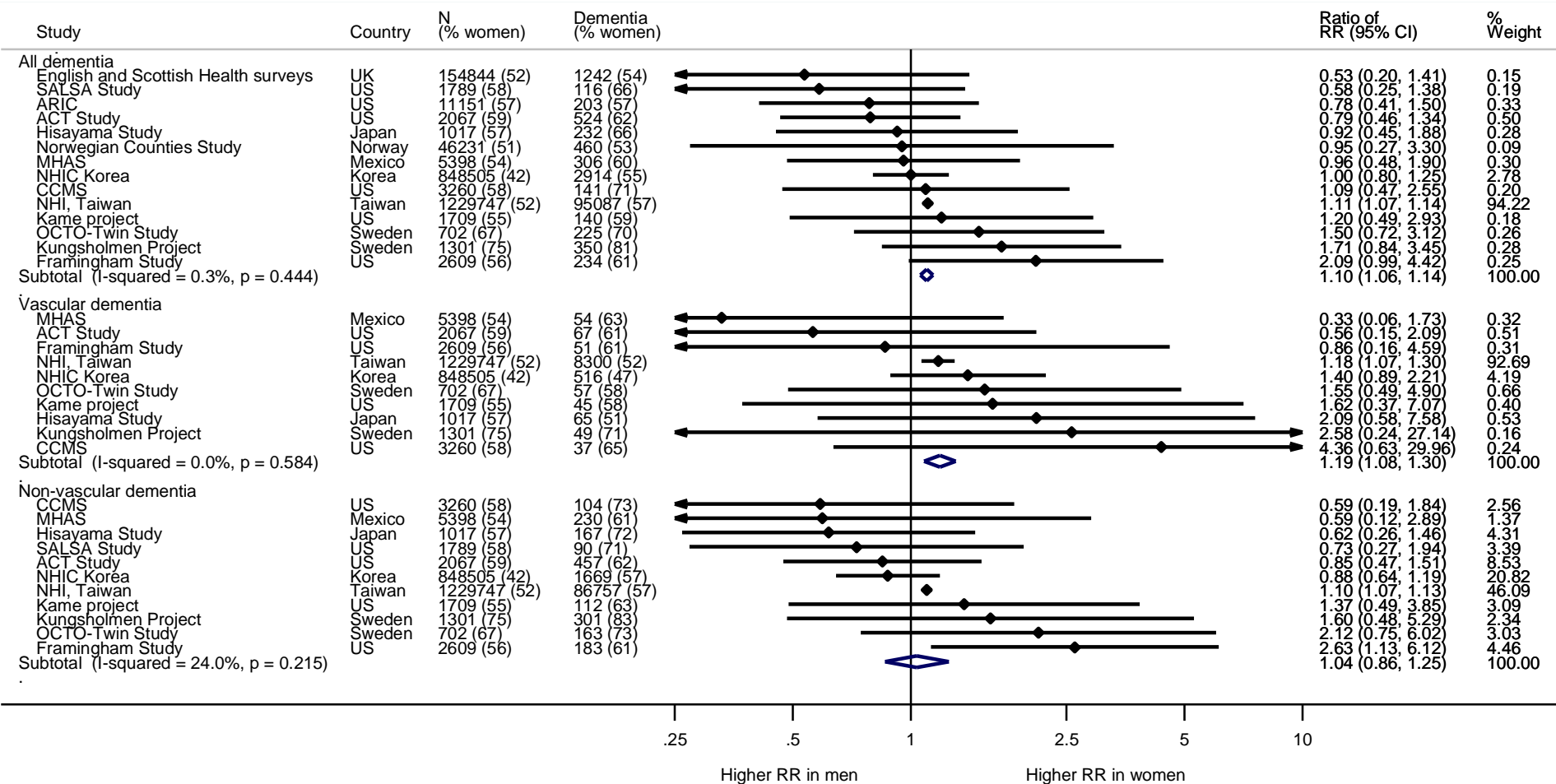
Cohort	Country	Baseline study (years)	Mean FU (years)	Age range (years)	N (% w)	N diabetes (% w)	N dementia (% w)	N VaD (% w)	N non-VaD (% w)	Ascertainment of diabetes	Ascertainment of dementia	Maximum adjustment available
Kame Project <sup>17</sup>	US	1992-1994	6	65+	1709 (55)	290 (44)	140 (59)	45 (58)	112 (63)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi
Kungsholmen Project <sup>25</sup>	Sweden	1987-89	9	75+	1301 (75)	104 (75)	350 (81)	49 (71)	301 (83)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi
MHAS <sup>22</sup>	Mexico	2001-03	3	60 +	5398 (54)	749 (61)	306 (60)	54 (63)	230 (61)	SR	CCCE, IQCODE	Age, hypertension, smoking, obesity
NHI, Taiwan <sup>12</sup>	Taiwan	2000-08	9	NR	1229747 (52)	614876 (52)	95087 (57)	8300 (52)	86757 (57)	Measured	ICD-9 codes	Age, insurance premium, region, urbanization cbvd, cvd, hypertension, hyperlipidemia
NHIC, Korea <sup>6</sup>	Korea	1992-95	14	40-95	848505 (42)	51611 (35)	2914 (55)	516 (47)	1669 (57)	Measured	DSM and medical examination	Age, alcohol
Norwegian Counties Study <sup>24</sup>	Norway	1974-78	35	35-50	46231 (51)	613 (34)	460 (53)	NA	NA	Measured or SR	ICD-9 codes	Age, sbp, smoking, bmi, tc
OCTO-Twin Study <sup>19, 21</sup>	Sweden	1991-99	9	80+	702 (67)	122 (67)	225 (70)	57 (58)	163 (73)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, bmi, tc
SALSA Study <sup>21</sup>	US	1998-99	10	60+	1789 (58)	797 (56)	116 (66)	12 (50)	90 (71)	Measured or SR	DSM, NINCDS/ADRDA,	Age, sbp, smoking, bmi, tc

Study abbreviations: %w; percent women; ACT, Adult Changes in Thought; ARIC, Atherosclerosis Risk in Communities Study; CCMS, Cache County Memory Study; MHAS, Mexican Health and Aging Study; NHI, National Health Insurance; NHIC, National Health Insurance Corporation; OCTO, Origins of Variance in the Old-Old; SALSA, Sacramento Area Latino Study on Aging.

Abbreviations: BMI, body mass index; CCCE, Cross-Cultural Cognitive Examination; cbvd, cerebrovascular disease; cvd, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Disease; IQCODE Informant Questionnaire on COgnitive Decline in the Elderly; NA, not available; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; sbp, systolic blood pressure; tc, total cholesterol, VaD, Vascular Dementia; SR, self-report diabetes; UK, United Kingdom; US, United States of America.







**Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people and more than 100,000 cases of dementia**

**SUPPLEMENTARY APPENDIX**

**Supplementary Methods: Newcastle - Ottawa Quality Assessment Scale**

Modified from reference 13

**Selection**S1) Representativeness of the exposed cohort

- a) truly representative of the general population\*
- b) somewhat representative of the general population
- c) selected group of users e.g. nurses, volunteers
- d) no description of the derivation of the cohort

S2) Selection of the non exposed cohort

- a) drawn from the same community as the exposed cohort \*
- b) drawn from a different source
- c) no description of the derivation of the non exposed cohort

S3) Ascertainment of exposure

- a) secure record (measured diabetes only) \*
- b) secure record or written self report
- c) written self report
- d) no description

S4) Demonstration that outcome of interest was not present at start of study

- a) yes \*
- b) no

**Comparability**C1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for age\*
- b) study also controls for systolic blood pressure, smoking, body mass index, and total cholesterol\*

**Outcome**O1) Assessment of outcome

- a) independent blind assessment of dementia and subtypes\*
- b) record linkage of dementia and subtypes\*
- c) self report
- d) no description

O2) Was follow-up long enough for outcomes to occur

- a) yes (at least 10 years) \*
- b) no

O3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for \*
- b) subjects lost to follow up unlikely to introduce bias - > 10% follow up, or description provided of those lost \*
- c) follow up rate < 90% and no description of those lost
- d) no statement

**Studies get a point for each \***



### Supplementary references

Note: In italics are the references to studies that had multiple reports from the same study.

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Supplementary Table 1: Quality assessment of the included studies

Study	S1	S2	S3	S4	C1	O1	O2	O3		Sum
ACT Study	1	1	1	1	1	1	0	1		7
ARIC Study	1	1	0	1	1	1	1	1		7
CCMS	1	1	0	1	1	1	0	1		6
English and Scottish Health Surveys	1	1	0	1	2	1	0	0		6
Framingham Study	1	1	1	1	2	1	1	1		9
Hisayama Study	1	1	1	1	2	1	1	1		9
Kame Project	1	1	0	1	1	1	0	1		6
Kungsholmen Project	1	1	0	1	1	1	0	1		6
MHAS	1	1	0	1	1	1	0	1		6
NHI, Taiwan	1	1	1	1	1	1	0	1		7
NHIC, Korea	1	1	1	1	1	1	1	1		8
Norwegian Counties Study	1	1	0	1	2	1	1	1		8
OCTO-Twin Study	0	1	1	1	2	1	0	1		7
SALSA	1	1	0	1	2	1	1	1		8

A description of the items for quality assessment is provided in the Supplementary methods

Supplementary Table 2: Incidence of dementia per 1000 person years by sex and diabetes status

	Women		Men		Differences		
	Diabetes	No diabetes	Diabetes	No diabetes	Women	Men	Women-Men
<b>Any dementia</b>							
ACT Study	34.75	36.38	39.63	32.4	-1.63	7.23	-8.86
ARIC	3.5	1.12	3.37	1.17	2.38	2.2	0.18
CCMS	17.22	12.14	11.75	6.53	5.08	5.22	-0.14
English and Scottish Health surveys	1.69	0.85	1.19	0.66	0.84	0.53	0.31
Framingham Study	17.53	11.28	11.25	10.46	6.25	0.79	5.46
Hisayama Study	29	21.32	23.46	15.3	7.68	8.16	-0.48
Kame project	22.76	13.03	17.03	11.39	9.73	5.64	4.09
Kungsholmen Project	104.3	65.61	51.65	46.11	38.69	5.54	33.15
MHAS	7.39	24.26	5.21	19.26	-16.87	-14.05	-2.82
NHI, Taiwan	13.38	8.71	10.97	7.52	4.67	3.45	1.22
NHIC Korea	NA	NA	NA	NA	NA	NA	NA
Norwegian Counties Study	0.705	0.326	0.683	0.319	0.379	0.364	0.015
OCTO-Twin Study	91.46	49.84	47.24	46.13	41.62	1.11	40.51
SALSA Study	13.74	10.34	11.99	5.44	3.4	6.55	-3.15
<b>Vascular dementia</b>							
ACT Study	5.21	4.45	8.16	3.75	0.76	4.41	-3.65
CCMS	10.6	2.23	2.94	2.18	8.37	0.76	7.61
Framingham Study	2.63	2.59	3.52	2.06	0.04	1.46	-1.42
Hisayama Study	8.12	4.33	7.33	6.56	3.79	0.77	3.02
Kame project	9.37	3.75	7.61	3.33	5.62	4.28	1.34
Kungsholmen Project	18.63	7.66	10.33	9.99	10.97	0.34	10.63
NHI, Taiwan	1.23	0.56	1.19	0.61	0.67	0.58	0.09
NHIC Korea	NA	NA	NA	NA	NA	NA	NA
OCTO-Twin Study	30.49	8.65	27.56	14	21.84	13.56	8.28
SALSA Study	1.06	0.82	2.77	NA	0.24	NA	NA
<b>Non-vascular dementia</b>							
ACT Study	29.54	31.93	31.47	28.65	-2.39	2.82	-5.21
CCMS	6.62	9.91	8.81	4.36	-3.29	4.45	-7.74
Framingham Study	14.9	8.69	7.74	8.39	6.21	-0.65	6.86
Hisayama Study	20.88	16.99	16.13	8.74	3.89	7.39	-3.5
Kame project	17.4	11.45	10.88	8.62	5.95	2.26	3.69
Kungsholmen Project	85.68	57.95	41.32	36.12	27.73	5.2	22.53
NHI, Taiwan	12.15	8.15	9.78	6.91	4	2.87	1.13
OCTO-Twin Study	61.02	39.13	19.69	32.13	21.89	-12.44	34.33
SALSA Study	11.63	8.43	6.92	4.6	3.2	2.32	0.88

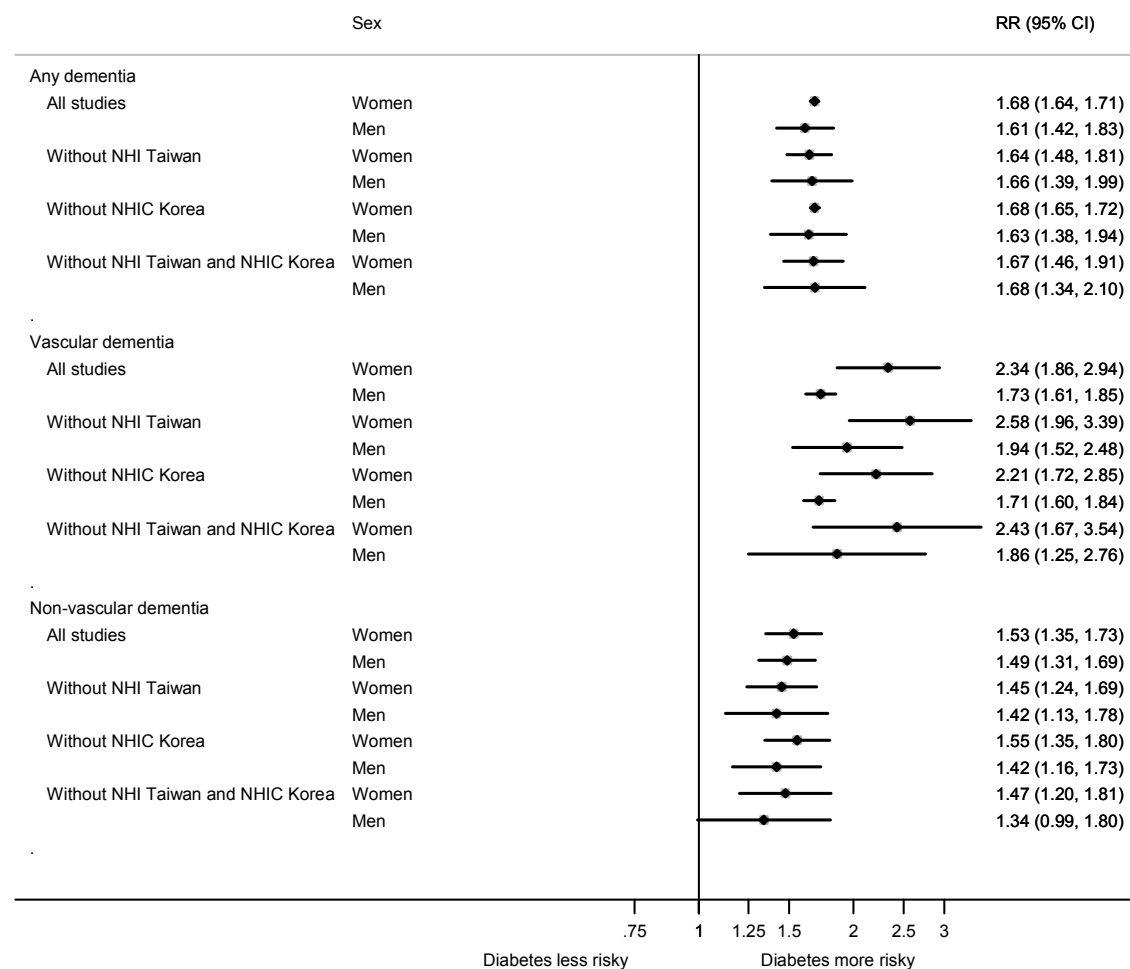
**SUPPLEMENTARY FIGURE LEGEND****Supplementary Figure 1**

Pooled multiple-adjusted relative risk for any dementia, vascular dementia and non-vascular dementia, comparing individuals with diabetes to those without diabetes, with and without exclusion of NHI Taiwan and NHIC Korea

**Supplementary Figure 2**

Pooled multiple-adjusted women to men ratio of relative risk for any dementia, vascular dementia and non-vascular dementia, comparing individuals with diabetes to those without diabetes, with and without exclusion of NHI Taiwan and NHIC Korea

Supplementary Figure 1



Supplementary Figure 2

